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# Treatment of Refractory Rheumatoid Arthritis — The Thalidomide Experience



OSCAR GUTIÉRREZ-RODRÍGUEZ, PÉRETZ STARUSTA-BACAL, and OSCAR GUTIÉRREZ-MONT

*Abstract.* In an open study, 17 patients (16 women, 1 man) with refractory or severe rheumatoid arthritis were treated with thalidomide. Two withdrew from the study in the first weeks. Thirteen patients received 531 ± 63 mg/day of thalidomide for 18.8 ± 8.8 weeks; in 2 the dose was 300 mg/day during 62 and 65 weeks. Seven patients attained complete remission, 5 partial remission, and the last 3 no improvement at all. Remissions lasted 6 years in 1 patient, 2 years in 3, 1 year in one, and varied between 8 months and 8 weeks in 7. After relapse, 5 patients received a 2nd course of treatment and attained remission again. This lasted 24, 10, and 9 months in 3; two are taking 100 mg/day of thalidomide as a maintenance dose and remain asymptomatic after 36 and 30 months. The side effects were drowsiness, constipation, hard swelling of the lower limbs, erythema of the face and limbs with local pruritus or burning sensation, hair loss, cough, nasal obstruction, fever, and skin and mucosal dryness. In 8 patients there was mild eosinophilia (<10%) and in 2 leukopenia. A 33-year-old woman showed amenorrhea up to 2 months after stopping treatment. After a 2nd course of treatment, 2 patients developed peripheral sensory neuropathy, which resolved spontaneously in 6 months. We believe these findings justify controlled trials with this agent. (*J Rheumatol 1989;16:158–163*)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS SEVERE REFRACTORY THALIDOMIDE

The treatment of rheumatoid arthritis (RA) is empirical; current measures include rest, physical therapy, supportive devices, the use of nonsteroidal antiinflammatory drugs (NSAID), and the so-called disease modifying drugs such as gold salts, penicillamine, levamisole or antimalarials. When patients do not respond to these measures and the disease continues its progressive course, it is considered intractable or refractory[1]. In such cases other measures have been tried: immunosuppressive drugs, plasmapheresis and lymphapheresis or total lymphoid irradiation; all are somewhat effective but, as yet, none can be recommended for general use[1]. Therefore, until a specific treatment based on a known cause is found, the search for better therapeutic agents continues.

erythrocyte sedimentation rate (ESR) and a decrease in rheumatoid factor (RF) titers, as reported in preliminary communications[7,8]. Observations are still under way, currently comprising 17 patients who had been treated with several NSAID and disease modifying drugs which had to be discontinued due to toxic effects or therapeutic failure.

## MATERIALS AND METHODS

Our study included 17 patients, 16 females and 1 male (Table 1), with clinical RA in 10 and definite RA in 7, according to the American Rheumatism Association criteria[9]. The age range was between 22 and 75 years (mean 48.3), and the duration of disease ranged from 8 months to 28 years (mean 122.3 months). Fourteen patients showed high titers of RF, while the remaining 3 were seronegative. Seven patients had subcutaneous nodules

based on the clinical and immunological similarities that exist between erythema nodosum leprosum and RA[2-4] and the known beneficial effects of thalidomide on patients with erythema nodosum leprosum[5,6], one of us (OGR) has been using thalidomide in the treatment of RA for the past 8 years with encouraging results; patients have obtained improvement of clinical signs and symptoms, with a decrease in the

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*Submitted August 8, 1988 revision accepted November 25,1988.*

and 2 had Sjögren's syndrome. Functionally, 3 belonged to class II, 6 to class III, and 8 to class IV[9]. All patients were receiving NSAID and had received disease modifying drugs which had to be discontinued because of toxic reactions or loss of effect; hence they were considered intractable or refractory. Four had been receiving prednisone, 10 mg or more/day for more than 1 year.

The investigation of all patients included a complete clinical history, examination, evaluation of the articular index (AI)[10], ESR (Westergren) and RF titration (latex fixation).

While treating the patient with NSAID, thalidomide was added at a dose of 300 mg/day (100 mg every 8 h) for 1-2 weeks. In the first 5 patients the dose was increased by 100 mg every 7-14 days, until the joint pain disappeared. This dose was maintained until local inflammation and ESR decreased. From that point on, thalidomide doses were progressively tapered until the drug was completely discontinued. Antiinflammatory agents were discontinued when the patients became asymptomatic. From the 6th patient onward, the dose of thalidomide was increased as of the 2nd week to 500-600 mg/day (Figure 1). Prednisone was reduced to 5 mg/day after completing the treatment with thalidomide in 3 patients, and it was discontinued later; one patient discontinued it completely in the 3rd week.

Table 1. *Clinical characteristics of patients with RA before treatment with thalidomide*

| Patients No. | Sex | Age (yr ± SD) | Disease Duration (mo ± SD | Type* | Functional Class* | Rheumatoid Factor** (n=14) | N | S |
|---|---|---|---|---|---|---|---|---|
| 17 | F, 16<br>M, 1 | 48.3 ± 11.8<br>(22–75) | 122.3 ± 82.1<br>(8–336) | C, 10<br>D, 7 | II, 3<br>III, 6<br>IV, 8 | 640<br>(80–10240) | 7 | 2 |

* ARA criteria.
** Latex fixation, tube dilutions, reciprocal of medium titer.
Ranges given in parentheses.
SD = standard deviation. F = female. M = male.
C = classic. D = definite. N = nodules.
S = Sjögren syndrome.

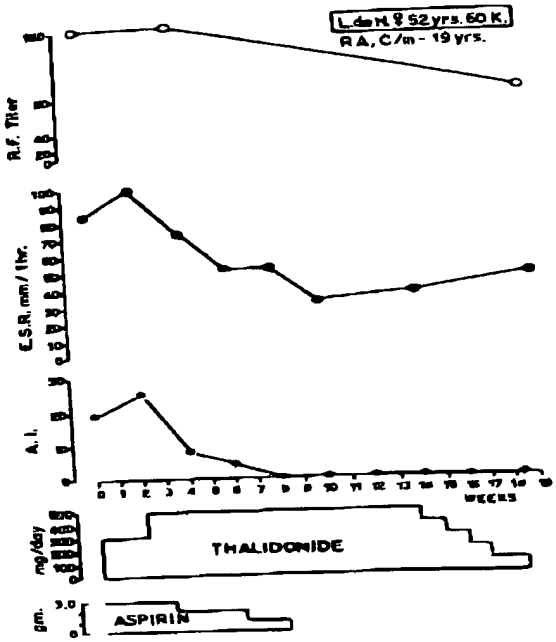


*Fig. 1.* Course of thalidomide treatment and response in Patient 12. Initially, the patient was taking aspirin, which was continued until joint pain disappeared. When thalidomide, 300 mg/day, was added, there was a brief early improvement followed by exacerbation of joint pains and acceleration of ESR; thalidomide dosage was increased after the 2nd week to 500 mg/day; the articular inflammation subsided and rapidly disappeared. ESR diminished but did not attain normal limits. Thalidomide dosage was progressively reduced and finally stopped. Fourteen weeks later the patient suffered a relapse and received a 2nd course of treatment which produced a new remission with normal ESR in 15 weeks. Since then, she is receiving 100 mg/day as a maintenance dose, and remains asymptomatic after 36 months.

Clinic visits were weekly for the first 2 weeks; then every 2 weeks until completion of the treatment, and then once a month for an indefinite period of time. Patients were instructed to consult immediately if they developed new symptoms or if they suffered an acute episode of arthritis. All patients were warned about the hazards of thalidomide in accordance with the Declaration of Helsinki and the Modification of Nurenberg, and the experimental nature of the trial was thoroughly explained, after which the patients were asked to sign an informed consent form. Of the 16 female patients, 10 were postmenopausal, 3 nuns, 1 had uterine agenesia, 1 had a tubal ligation, and one was a virgin.

Two patients withdrew from the study. The first, a 40-year-old seronegative man had been receiving 10–20 mg prednisone daily for more than one year. Having shown an early improvement, he discontinued the prednisone in the 3rd week. By the 5th week he developed severe vomiting and had to discontinue thalidomide and resume taking prednisone on the 7th week. The second patient, a 75-year-old woman, seronegative, with a 28-year history of RA, refused to go beyond 300 mg thalidomide daily, due to drowsiness, and she withdrew from the study at the end of the 6th week. Fifteen female patients remained in the study, of whom 14 were seropositive and 1 seronegative.

In 5 patients whose symptoms relapsed after periods of remission lasting from 2 to 25 months, a second course of thalidomide treatment was prescribed. Two of them continued taking 100 mg of thalidomide/day, after a new remission, as a maintenance dose.

*Dose and duration of treatment.* Five patients received thalidomide 600 mg/day; in 7 the dose was 500 mg, and one patient whose weight was 42.5 kg received 400 mg/day. In these 13 patients the mean dose was 531 ± 63 mg/day. In terms of body weight, the doses ranged from 6.9 to 15 mg/kg/day (mean 10 ± 2.4 mg). The duration of treatment ranged from 7 to 38 weeks (mean 18.8 ± 8.8). The other 2 patients showed marked drowsiness and, for this reason, they took only 300 mg daily (4.9 and 6.4 mg/kg/day) for 62 and 65 weeks, respectively.

*Statistical analysis.* Wilcoxon's nonparametric method was used to analyze the paired data for each assessment method, that is, initial and final values obtained after discontinuing the drug. Values are given as mean ± standard deviation.

## RESULTS

In 12 patients the pain disappeared several weeks after the onset of treatment with thalidomide. Joint swelling and other inflammatory phenomena subsided later on, reaching an AI of 0 (Figure 2), and morning stiffness disappeared. In another seronegative patient who had received prednisone for a long time but had discontinued it 2 months before, we noted both a marked improvement and a decrease in the AI; however, her knees and wrists showed persistent inflammation, and there was abundant joint effusion in her knees which reappeared after 3 taps. Both knees showed prominent synovial pannus formation, and on radiographs there was evidence of advanced joint destruction. The 2 patients who received only 300 mg of thalidomide daily, showed an initial improve-

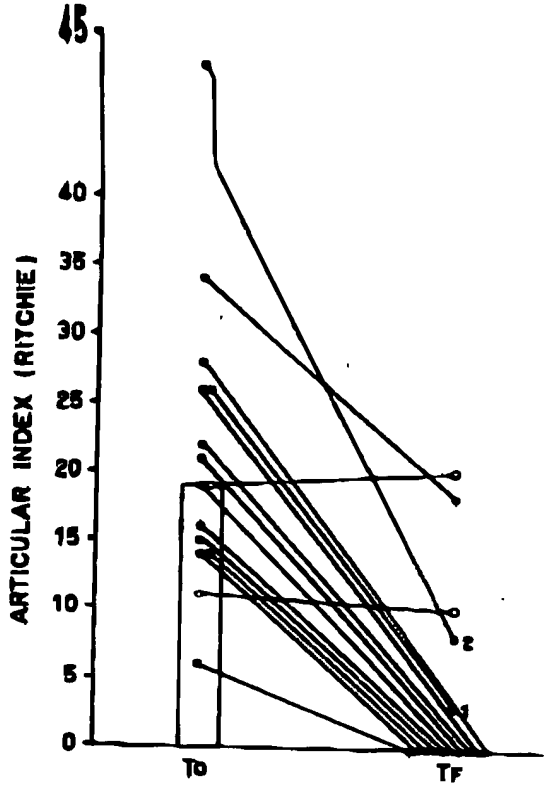


*Fig. 2.* The effect of thalidomide on articular index in 15 female patients with RA.
TO = initial time, before treatment. TF = final time, end of treatment. The interval between TO and TF ranged from 7–38 weeks (mean 18.8 ± 8.8) in 13 patients (●——●). In 2 patients (○——○) it was 62 and 65 weeks. Median, before treatment = 19; after treatment = 0. N = 15; T = 1.5; Z = 3.43; $p < 0.01$.
Four weeks later, AI had decreased to 0, (2) 6 weeks later, AI had decreased (1) to 0.

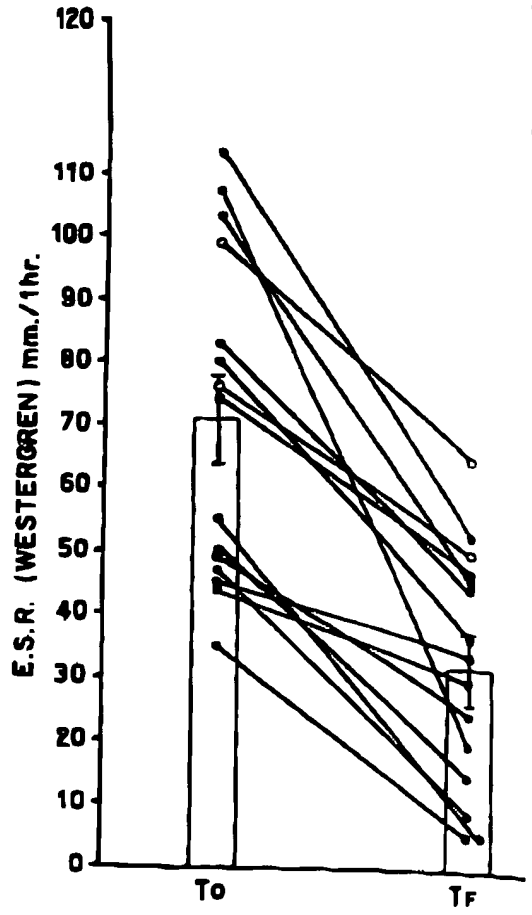


*Fig. 3.* The effect of thalidomide on ESR in 15 female patients with RA
TO = initial time, before treatment. TF = final time, end of treatment
The interval between TO and TF ranged from 7–38 weeks (mean 18.8 ± 8.8) in 13 patients (●——●); in 2 patients it was 62 and 65 weeks (○——○)
Mean, before treatment = 70.7 ± 6.8 mm/h; after treatment = 32.5 ± 4.8 mm/h.
t distribution in paired samples = 7.62 (GL = 14) $p < 0.01$.

ment of pain and joint inflammation. Nevertheless, these symptoms worsened again a few weeks later, and they persisted although the drug was being taken on a continuous basis.

The ESR became normal in 7 patients[11], and it showed a marked decrease in the remaining 8 (Figure 3). Of the 14 seropositive patients, 3 became negative, 10 showed a decrease in RF titers, and one showed no change (Figure

weeks. The remaining 4 patients relapsed after 24, 15, 14 and 8 weeks. Five patients received a 2nd course of treatment after which 3 of them had remissions lasting 24, 10 and 9 months. In the remaining 2, who are still taking 100 mg thalidomide daily, an improvement has been sustained

4). Hemoglobin increased in 11 patients, and body weight in 10. Rheumatoid nodules disappeared in 4 patients and decreased in size in 3. The 2 patients with Sjögren's syndrome showed an increase in salivary and tear secretion, with an improvement in Schirmer's test. Most of the patients developed an exacerbation of symptoms with an increase in the ESR on the 2nd and 3rd weeks of treatment, but these phenomena were transient and subsided by continuing treatment and increasing the dose of thalidomide (Figure 1).

*Duration of remissions.* The duration of remissions has been variable. One patient continues to be free of symptoms 6 years after the end of treatment. Two patients were asymptomatic after 2 years, but they have been lost to followup. One patient relapsed after 25 months. In one patient symptoms recurred after one year, and in another one after 8 months. Two patients are still free of symptoms after 25 for 36 and 30 months.

*Side effects.* Various types of side effects were seen (Table 2). All patients showed drowsiness, which was severe in some cases. Constipation, another constant effect, was controlled with bisacodyl suppositories, but in some cases thalidomide had to be discontinued for 24–48 h in order to achieve a bowel movement. Eight patients developed macular or maculopapular erythema of the face and limbs, with itching or burning sensation, and another 2 showed a scarlatiniform rash with desquamation of the palms and soles. Eight patients developed hard edema of the lower limbs until the end of treatment, with spontaneous remission upon discontinuation of the drug. Seven patients showed abundant hair loss after the 6th week of treatment, but not to the point of alopecia. Three patients had an increase in bronchial secretions, with bronchospasm and severe coughing. Three

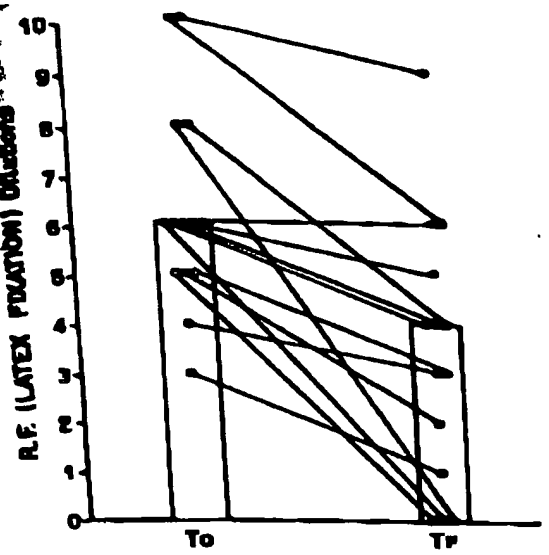


Fig. 4. The effect of thalidomide on RF in 14 seropositive female patients with RA.
Median, before treatment (To) = 6, after treatment (Tf) = 4
N = 14; T = 0; Z = −3.17; p < 0.01.

Table 2. *Side effects of thalidomide treatment in 15 patients with RA*

| Complication | No. |
|---|---|
| Drowsiness | 15 |
| Constipation | 15 |
| Eosinophilia | 9 |
| Swelling, lower limbs | 8 |
| Erythema, face, and limbs | 8 |
| Increased hair loss | 7 |
| Skin and mucosal dryness | 5 |
| Pruritus | 4 |
| Nasal obstruction, rhinorrhea | 4 |
| Fever | 3 |
| Bronchitis | 3 |
| Nausea, vomiting | 2 |
| Desquamation, palms, and soles* | 2 |
| Leukopenia | 2 |
| Atypical lymphocytes | 2 |
| Peripheral sensory neuropathy | 2 |
| Amenorrhea | 1 |
| Herpes zoster | 1 |

* These 2 patients presented scarlatiniform rash.

patients developed fever of up to 39°C (102°F) on several occasions during the treatment period. Several patients complained of nasal obstruction with rhinorrhea, nausea, and vomiting, in addition to dryness of skin and mucosae. Nine patients developed moderate eosinophilia (< 10%). Two patients developed leukopenia: one of them had 3400 white blood cells/mm³ while taking 600 mg thalidomide daily (15 mg/kg/day). When the dose was decreased to 400 mg (10 mg/kg/day) the white cell count became normal. The other patient showed 3500 white cells/mm³; one week later the white count returned to normal, with no change in the dose (500 mg: 9.2 mg/kg/day). Two patients showed atypical lymphocytes on the peripheral blood smear. One patient developed an episode of intercostal herpes zoster. Another patient, 33 years old, had amenorrhea for 6 months; menstrual cycles were resumed 2 months after discontinuing thalidomide.

Two of the patients who received a second course of treatment (30 and 31 weeks long), developed peripheral sensory neuropathy, with a prickling and stinging tingle of the limbs. There were no motor disturbances or reflex alterations. These effects decreased a few weeks after discontinuing thalidomide, to disappear completely after 6 months with no therapy at all.

## DISCUSSION

Of 17 patients with severe RA who were treated with thalidomide, 2 withdrew within the first 6 weeks. Of the remaining 15 patients, 7 experienced complete remission with disappearance of pain, inflammation and joint stiffness and a return to a normal ESR[11]; 5 patients attained partial remission. One patient showed marked amelioration of symptoms and 2 showed only a mild improvement at the beginning of therapy, but they returned later on to their initial status. The RF which was positive in 14 patients became negative in 3, decreased in 10, and remained unchanged in 1. Subcutaneous nodules, present in 7 patients, disappeared in 4 and decreased in size in 3. The 12 patients who showed remission received doses ranging from 400 to 600 mg/day (mean 531 ± 63 mg). These body weight related doses ranged from 6.9 to 15 mg/kg/day (mean 10 ± 2.4 mg). In the 2 patients who showed no improvement, the dose was 300 mg (4.9 and 6.4 mg/kg/day, respectively). The duration of remissions has been variable, being shorter in patients who had been taking corticosteroids.

The mechanism of action of thalidomide has not been completely established. It inhibits neutrophil chemotaxis[12,13], decreasing phagocytic activity and antagonizing prostaglandins $E_2$ and $F_2\alpha$, acetylcholine, histamine and 5-hydroxytryptamine[12]. It decreases monocyte phagocytosis[14], but increases chemotaxis and superoxide release[15]. Miyachi, on the other hand[16], suggests that thalidomide decreases the generation of superoxide and hydroxyl radicals by polymorphonuclear leukocytes, thus preventing tissue damage.

It has been shown, too, that thalidomide has an effect on several immunologic variables, including inhibition of blastic transformation induced by phytohemagglutinin in human cultured lymphocytes[17], prolongation of the survival time of

skin homografts in mice[18], and decreased proliferation of immunoblasts in regional lymph nodes[19]. In addition, it reduces the severity of the graft-versus-host reaction[20], and significantly diminishes the intensity of adjuvant disease of rats[21]. In rabbits injected with incompatible erythrocytes, thalidomide inhibits the production of isoantibodies[22]; in mice immunized with sheep erythrocytes, thalidomide blocks IgM antibody synthesis[12,23], and in patients with leprosy treated for erythema nodosum leprosum it determined a selective decrease in the concentration of serum IgM[29].

Most patients showed an exacerbation of pain and an increase in ESR during the first weeks of treatment (Figure 1). These phenomena as well as some side effects, such as constipation, leg swelling, skin erythema, pruritus, nasal obstruction, eosinophilia, and bronchospasm, lead us to assume that there is a release of chemical mediators of anaphylaxis, e.g., prostaglandins, kinins, histamine, serotonin, leukotrienes, and eosinophil chemotactic factor. Some of these phenomena, in fact, disappear with the use of aspirin or other cyclooxygenase inhibitors and antihistamines.

The sometimes severe drowsiness which led to the withdrawal of one patient and the refusal of 2 to increase the dose, was actually the initial indication of thalidomide, since it was introduced as a hypnotic and sedative agent[24]. Some patients complained of insomnia for several days after discontinuation of the drug. Peripheral sensory neuropathy constitutes a serious complication, sometimes of early appearance[25], although initially it had been seen only after several months of treatment[24]. This effect has been considered refractory to any type of therapy; however, our 2 patients had spontaneous regression upon discontinuation of the drug, and they had no further sequelae.

Hematologic effects have been minimal: we have seen only 2 cases of readily reversible leukopenia. We did not see any platelet changes. No changes in renal function were found in these patients. Otherwise, thalidomide is a safe medication which does not cause cardiac or respiratory depression. Its acute toxicity is minimal, if we take into account that subjects who ingested 14 and 14.4 g for suicidal purposes, developed only profound somnolence waking up in less than 24 h without further sequelae[24].

In view of the fact that several authors had reported the appearance of myxedema during therapy with thalidomide[24], T3, T4, and TSH tests were performed in 3 of our patients, after discontinuing the medication, yielding normal results.

Bearing in mind the tremendous teratogenic effects of thalidomide, which caused the birth of several thousand infants with phocomelia between 1958 and 1962[24], its administration ought to be restricted to males and menopausal females, avoiding its use, by all means, in women with the risk of becoming pregnant. In women of child bearing age, thalidomide may be used only when adequate contraceptive measures have been taken.

Based on the results of our study, controlled studies sus placebo appear to be indicated, although the fre of some side effects, as drowsiness and constipation, render double blind studies difficult.

## ACKNOWLEDGMENT

We are indebted to Reynaldo Carvajal-Ortiz, Lic, BMF, for kindly per the statistical analysis of the data, and to Dr. Matilde de Bernal for ing out the thyroid hormone studies.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: A61K 31/445, 31/52, 31/57, 31/665 — A2

(11) International Publication Number: WO 95/04533

(43) International Publication Date: 16 February 1995 (16.02.95)

(21) International Application Number: PCT/US94/08742

(22) International Filing Date: 3 August 1994 (03.08.94)

(30) Priority Data: 08/101,724 — 4 August 1993 (04.08.93) — US

(61) Designated States: AU, CA, CN, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
*Without international search report and to be republished upon receipt of that report.*

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(54) Title: TREATMENT OF RHEUMATOID ARTHRITIS WITH THALIDOMIDE ALONE OR IN COMBINATION WITH OTHER ANTI-INFLAMMATORY AGENTS

(57) Abstract

The present invention relates to a novel method for treating rheumatoid arthritis with thalidomide alone or in combination with anti-rheumatoid agents and/or with steroidal and/or non-steroidal anti-inflammatory drugs. The present invention also relates to methods of treating rheumatoid arthritis with tumor necrosis factor inhibitors as well as pharmaceutical compositions containing tumor necrosis factor inhibitors and steroidal and/or non-steroidal anti-inflammatory and/or anti-rheumatoid drugs. A further aspect of this invention relates to a special pharmaceutical composition containing thalidomide wherein said thalidomide has been micronized to a particle size of less than 1.0 microns. Compositions containing such micronized thalidomide exhibit faster absorption rates than previously known thalidomide formulations.

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WO 95/04533 PCT/US94/08742



# TREATMENT OF RHEUMATOID ARTHRITIS WITH THALIDOMIDE ALONE OR IN COMBINATION WITH OTHER ANTI-INFLAMMATORY AGENTS

The present invention relates to a novel method for treating rheumatoid arthritis with thalidomide alone or in combination with anti-rheumatoid agents and/or with steroidal and/or non-steroidal anti-inflammatory drugs. The present invention also relates to methods of treating rheumatoid arthritis with tumor necrosis factor inhibitors as well as pharmaceutical compositions containing tumor necrosis factor inhibitors and steroidal and/or non-steroidal anti-inflammatory and/or anti-rheumatoid drugs. A further aspect of this invention relates to a special pharmaceutical composition containing thalidomide wherein said thalidomide has been micronized to a particle size of less than 1.0 microns. Compositions containing such micronized thalidomide exhibit faster absorption rates than previously known thalidomide formulations.

## DESCRIPTION OF THE PRIOR ART

Thalidomide was first synthesized and marketed in Germany in the 1950's as a sedative. The toxicity of the compound was so low that a dose killing 50% of animals ($LD_{50}$) could not be established. Thalidomide therefore, promised to be a safer alternative to the use of Barbiturates. In 1961 Thalidomide was realized to be responsible for an epidemic of malformations. The incidence of malformed babies paralleled the sales of thalidomide preparations and dropped to the extremely low values of the pre-thalidomide era after the drug was withdrawn from the market.

Oral administration of thalidomide in the range of 100 to 200mg in humans results in maximal blood concentration of 0.9 to 1.5mg/L after 4 to 6h. The hydrolytic cleavage in serum is much slower than *in vitro* at pH 7.4. This may be because thalidomide is highly bound to plasma proteins. Studies and experimental animals showed high concentrations of the drug in the gastrointestinal tract, liver and kidney, and lower concentrations in muscle, brain

and adipose tissue. In pregnant animals, thalidomide is able to pass across the placental barrier.

Although total studies of thalidomide metabolism in humans do not exist, in animals the main pathway of degradation appears to be nonenzymatic hydrolytic cleavage. The biochemical mechanism of non-sedative effects of thalidomide is unclear. Very little work has been done to understand the immunomodulatory effect of the compound on a molecular basis.

The current therapeutic uses of thalidomide include the following: acute and Chronic Graft-Versus-Host-Disease, Aphthosis, Cold hemagglutinin disease, Colitis, Cutaneous lupus erythematosus, Erythema nodosum leprosum, Erythema multiform, Histiocytosis, Immune complex vasculitis, Jessner-Kanof's disease, Lichen planus, Pemphigoid disorders, Photodermatoses, Prurigo nodularis, Pyoderma gangraenosum, Rheumatoid arthritis, Sarcoidosis, and Weber-Christian's disease as well as HIV *in vitro*.

Rheumatoid arthritis is a chronic, progressive, inflammatory arthritis involving multiple joints, characterized by a tendency to spontaneous remissions and subsequent relapses. Within the context of the present application, rheumatoid arthritis (RA) is defined to also include juvenile rheumatoid arthritis. Rheumatoid arthritis has many manifestations which affect different parts of the body. One simple definition is that rheumatoid arthritis is a disease of articular joints in which the cartilage and bone is slowly eroded away by a proliferative, invasive connective tissue called panus, which is derived from the synovial membrane and may involve peri-articular structures such as bursae, tendon sheets, and tendons as well as extra-articular tissues such as the subcutaneous, cardiovascular system, lungs, spleen, lymph nodes, skeletal muscles, central and peripheral nervous systems, and the eyes. Typical symptoms which are indications of a poor-prognosis are subcutaneous nodules, vasculitis, neuritis, cardiopulmonary disease, pericarditis, Sjogren's syndrome, and Feltys syndrome. Ancillary abnormalities of the disease include anemia, elevated erythrocytes sedimentation rate (ESR), high titer serum rheumatoid factor (RF), and

inflammatory synovial fluid. Affected bone is demineralized, eroded, and then deformed. The origin of rheumatoid arthritis is as yet not fully understood.

Recent studies suggest involvement of both humoral and cell-mediated immune responses in the underlying chronic inflammatory reaction occurring in the joint. Tumor necrosis factor has been also implicated in rheumatoid arthritis disease. Rheumatoid factor is the most widely recognized serum marker in rheumatoid arthritis. In one scenario, a virus, a small bacterium, or some other agent induces an inflammatory defense response that persists in some patients. By-products of the immune reaction inflame the synovium and trigger the destructive joint changes which cause pain, stiffness, functional impairment and fatigue in patients.

Evidence of the proximal molecular and or cellular cause of rheumatoid arthritis and, therefore, prospective targets of thalidomide action is diverse. Myachi found that thalidomide decreased generation of superoxide and hydroxide radicals in the synovial fluid of rheumatoid arthritis patients. He proposed that thalidomide may act by reducing these polymorphonuclear leukocyte generated oxygen radical intermediates which are significantly increasing in the synovial fluids.

Iwakura reports evidence that implicates HTLV-1 as an etiological agent in the development of rheumatoid arthritis. Marrack reports that V$\beta$ 14+ T-cells were prevalent in the synovial fluid of rheumatoid arthritis patients and implicates them in the etiology of rheumatoid arthritis.

Sigler has identified high concentrations of the enzyme phospholipase $A_2$ ($PLA_2$)in the synovial fluid of patients with rheumatoid arthritis. $PLA_2$ is secreted in response to tumor necrosis factor; its hydrolysis of phosphoglycerides to release arachidonate is the rate determining step in the production of eicosanoid mediators of inflammation. Therefore, tumor necrosis factor and/or $PLA_2$ may play key roles in inflammation and the ability of thalidomide to prevent production or action of tumor necrosis factor may inhibit the phosphoglyceride-arachidonate-eicosanoid inflammatory cascade.

To date, the different treatments of rheumatoid arthritis have proved unsatisfactory. Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and aspirin-like drugs are used for the symptomatic treatment of RA in humans. Steroids have also been used. However, while steroids provide symptomatic relief, they do not prevent destruction caused by arthritis. Steroids can also lead to diabetes, cataracts, and increased rate of infections. Additionally, there is often a rapid reappearance of the active disease when treatment is ended. On the other hand, clinicians over the years have used a number of drugs which they argue reduces the rapid progression of rheumatoid arthritis. These drugs are termed "fundamental" or "disease-modifying drugs", or "disease-modifying anti-rheumatic drugs." These drugs include for example; gold salts; metal chelators such as D-penicillamine; antimalarial drugs such as chloroquine, dapsone, and sulfasalazine.

Cytotoxic and immunosuppressive drugs have also been used to control rheumatoid arthritis. Methotrexate and cyclophosphate are both immunosuppressive and cytotoxic. The immunosuppressive drugs include cyclosporin and corticosteroids.

Gutierrez-Rodriguez reports that use of 400 to 600mg per day of thalidomide for 7 to 20 weeks in seven patients, in some cases in conjunction with aspirin or prednisone, causes decrease, normalization or elimination of pain, a decrease in erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF) titers in some or all patients. In a later report Gutierrez-Rodriguez reports that of 15 patients receiving thalidomide at a dosage of 400 to 600mg per day for 7 to 38 weeks (in two patients 300mg per day 62 and 65 weeks), seven achieved complete remission with disappearance of pain, inflammation, joints stiffness and abnormal ESR. Five achieved partial remission and three showed no improvement. Of five relapses, all reattained remission, three of four for nine to twenty-four months on induction therapy and 2 for 30 to 36 months on induction therapy followed by maintenance therapy of 100mg per day. All told, pain disappeared in 12 of 15 patients; RF became negative in 3 of 4 cases, decreased

in 10 of 14, showed no change in 1 of 14; ESR became normal in 7 of 15 and markedly decreased in 8 of 15 and the articular index (AI) reached zero in 10 of 15 and sharply decreased in 5 of 15 patients.

## SUMMARY OF THE INVENTION

The primary object of the present invention is to provide a method for the treatment of rheumatoid arthritis with tumor necrosis factor inhibitors.

A further object of the present invention is the treatment of rheumatoid arthritis with thalidomide, alone and in combination with steroidal anti-inflammatory agents and/or nonsteroidal anti-inflammatory agents and/or anti-rheumatoid agents.

Another object of the present invention is to provide a method for treating rheumatoid arthritis with thalidomide at a given regimen.

An additional object of the present invention is to provide compositions of matter comprising tumor necrosis factor inhibitors with non-steroidal anti-inflammatory drugs and/or steroidal anti-inflammatory drugs and/or antirheumatic drugs.

Still another object of the present invention is to provide a composition of matter containing thalidomide having a specific particle size.

A further object of the present invention is to provide a thalidomide or tumor necrosis factor inhibitor mediated therapy in which dosages of other drugs can be substantially reduced.

A still further object of the present invention is a method for the therapeutic treatment of rheumatoid arthritis which comprises treatment with thalidomide and other drugs on alternate days (by diverse schedules).

## DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention deals with a treatment of rheumatoid disorders which comprises administering to a patient in need of such treatment, a daily dosage form during an uninterrupted consecutive sequence of 365 days, and in

accordance with the following regimen: (a) a three time a day, oral dose in an uninterrupted consecutive sequence of not more than 365 days of a tumor necrosis factor inhibitor compound effective in the treatment of rheumatoid disorders in dosage amounts not to exceed 900mg per day or until RF or ESR have decreased or returned to normal, and (b) a daily, oral dose in uninterrupted consecutive sequence after cessation of said regimen (a) of a tumor necrosis factor inhibitor compound effective in the treatment of rheumatoid disorders in dosage amounts of less than or more than 100mg/day indefinitely or until RF or ESR stabilize or normalize.

The present method of administration of tumor necrosis factor inhibitor such as thalidomide is a significant improvement over the prior art method of treating rheumatoid arthritis published by Gutierrez-Rodriguez. Gutierrez-Rodriguez looked at a narrow range of doses of thalidomide against RA (400-600 mg) for no more than 38 weeks (exclusive of a 300 mg dose for 65 weeks). Gutierrez-Rodriguez also permitted patients to continue taking aspirin or prednisone so that additive or synergistic effects with thalidomide cannot be ruled out.

The following invention teaches the following items which Gutierrez-Rodriguez did not consider.

1. Treatment doses less than 300 mg or greater than 600 mg.
2. Treatment duration longer than 38 weeks (65 weeks).
3. Elimination of all other drugs (aspirin, steroids) to ensure measure of effectiveness is of thalidomide alone.
4. Maintenance doses less than or more than 100 mg/day.
5. Maintenance durations longer than 65 weeks.

The methods of the invention include administering to an animal afflicted with a disease arising from an abnormal or undesirable normal immune response (for example, rheumatoid arthritis) an affecting amount of a tumor necrosis factor inhibitor, or a combination of two or more tumor necrosis factor inhibitors, or combinations of tumor necrosis factor inhibitors with anti-inflammatory drugs.

The animal can further be treated with other disease-modifying anti-rheumatic drugs, cytotoxic drugs, immunosuppressive drugs, and/or steroids. These treatments are to either prevent, ameliorate and/or retard the disease in its progression in the afflicted animal.

Efficacy in control of symptoms was evaluated by interviewing the patients subjective experiences of the severity of symptoms on a three-graded scale: mild-moderate-severe.

In another preferred embodiment of the present invention, thalidomide is micronized to a particle size less than 1.0 microns. Thalidomide having this particle size has a much more effective absorption rate than thalidomide of the prior art.

Another preferred embodiment of the present invention are combinations of tumor necrosis factor inhibitors with non-steroidal anti-inflammatory carboxylic acids. Typical tumor necrosis factor inhibitors which can be used with the present invention include thalidomide, pentoxifylline, and xanthine derivatives.

The preferred non-steroidal carboxylic acids include the aryl acetic acids, the fenamic acids, the aryl propionic acids, the biphenyl carboxylic acids, and the diphenyl ether carboxylic acids.

The preferred acetic acids include indomethacin, acemetacin, cirunetacin, suldindac, tolmetin, zomepirac, diclofenac, fenclofenac, isoxepac, furofenac, fentiazac, clidanac, oxepinac, fenclorac, ionazolac, metiazinice acid, clopirac, amfenac, benzofenac, clometacine, etodolac, bumadizone, and clamidoxic acid.

The preferred aryl propionic acids include ibuprofen, flurbiprofen, naproxen, ketoprofen, fenoprofen, benoxaprofen, indoprofen, pirprofen, caprofen, oxaprozin, pranoprofen, suprofen, miroprofen, tioxaprofen, alminoprofen, cicloprofen, tiaprofenic acid, furaprofen, butibufen, fenbufen, furobufen, bucloxic acid, and protizinic acid.

The fenamates acids includes mefenamic acid, flufenamic acid, meclofenamate, niflumic acid, tolfenamic acid, flunixin and clonixin.

Anti-rheumatic agents which may be used in combination with tumor necrosis factor inhibitors include gold salts such as aurinofin and include the penicillamines.

Additional compositions include TNF inhibitors and steroidal anti-inflammatories such as prednisone.

The following are illustrative examples of the present invention.

EXAMPLE I

The following illustrate the micronization of thalidomide. Thalidomide is micronized using a micronizer to a particle size less than one micron, i.e., 0.5 microns.

EXAMPLE II

100mg of thalidomide and 200mg of ibuprofen are mixed. The active ingredients are triturated and Q.S. with lactose to selected capsule size.

EXAMPLE III

300mg thalidomide are mixed with 350mg of naproxen. The active ingredients are triturated Q.S. with lactose to selected capsule size.

EXAMPLE IV

500mg thalidomide are mixed with 200mg indomethacin. The active ingredients are triturated Q.S. with lactose to selected capsule size.

EXAMPLE V

Methods of treatment of rheumatoid arthritis.

The following example shows how both compounds and their compositions can be used in treating diseases arising from abnormal or undesirable normal immune responses. Preferably these diseases are autoimmune diseases. More preferably, the autoimmune disease is rheumatoid arthritis. The

compounds and their compositions can be used to eradicate or reduce the severity of rheumatoid arthritis. Briefly, the afflicted animal is administered an effective amount of thalidomide or a combination of thalidomide with a steroidal or a non-steroidal anti-inflammatory drug or anti-rheumatoid agent. Then both compounds can be administered individually or combined into compositions. The compounds in combinations are hereinafter referred to as compounds. The preferred animal subject is human. The animal can further be treated with disease modifying anti-rheumatic drugs, cytotoxic drugs, immunosuppressive drugs and/or steroids.

The strategy used in treating a particular animal patient depends on his species, age, general health, status of rheumatoid arthritis, etc. For example, the desired dose of compound may be presented as 2,3,4 or more sub-doses administered as infusions or taken orally at appropriate intervals throughout a treatment period. If administered as infusion, administration is by any suitable route such as parenteral (including subcutaneous, intramuscular, intravenous and intradermal). The preferred route is orally in the form of including, but not limited to, tablets or capsules. For example, the patient could take effective doses of thalidomide and ibuprofen tablets or capsules three times a week. It would be appreciated that the preferred route may vary based on the factors discussed above.

Additional combination chemotherapy which can be used with tumor necrosis factor inhibitors include compounds such as gold salts, metal chelators, anti-malarials, dapsone, sulfasalazine, and other traditional or new drugs used in the treatment of rheumatoid arthritis. If one of the drugs has side effects, it can be given to patients on alternate treatment periods. Additionally, in combination, the different drugs in the compounds may exert a synergistic effect. Further, the toxicities of the drugs may also be separate and not additive. There can be a trade-off between the toxicity and effectiveness of the drugs.

While the compounds may be administered alone, they may be presented as part of a pharmaceutical formulation. Preferably, compounds are combined with an acceptable carrier. The formulations of this invention may include other

agents conventional in the art having regard to the type of formulation in question. The formulations can also include other anti-rheumatoid drugs, immunosuppressive drugs and/or steroids. The carrier must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient.

The following is an example of a procedure for administering a formulation containing thalidomide and ibuprofen to a human patient: The patient takes a tablet or capsule containing 300 mg of thalidomide and 100 mg of ibuprofen three times a day. Dosage may be increased by 50 mg of each of the components every two to three weeks. The maximum level of dosage is determined at the point at which unacceptable toxicity first occurs or the patient shows improvement. At the end of the five-day period, the patient is evaluated. The evaluation includes physical examination and extensive laboratory testing. The testing also includes evaluation for toxicity, including somnolence, peripheral neuropathy and constipation. Additional laboratory monitoring includes complete blood cell count every two weeks and then monthly thereafter.

The dosage will be varied by taking into consideration the individual patient's tolerance of the drug, its efficacy and toxicity. Other anti-arthritis drugs mentioned above can be used in combination with the treatments. According to the results of the test, a starting dose of a particular compound is reduced for a patient who exhibits adverse reaction or the drug used in combination with the compounds can be changed or reduced.

The test for monitoring the improvement of the disease can include specific tests-directed, for example, to determination of systemic response to drug(s) which includes erythrocyte sedimentation rate (ESR), articular index (AI), rheumatoid factor (RF) and acute phase reactants (APR) observations are made of the swelling, etc., of the afflicted body parts. Improvement in stiffness, grip and pain of the patient is also observed. If the patient's condition is stable, he is re-treated at the same dosage weekly and evaluated weekly or at lesser dosage(s) if toxicity has occurred. Provided a patient's condition is stable, the

treatment may be continued. After six months of treatment, anatomical changes of skeleton is determined by radiologic imaging, for example, by x-ray radiography.

At the end of each period, the patient is again evaluated. Comparison of the pre-treatment and post-treatment radiological assessment, ESR, AI, RF and acute phase reactants indicate the efficacy of the treatments. According to the efficacy of the treatments, in the patients condition, the dosages of the components in the formulations may be increased or maintained constant for the duration of treatment.

EXAMPLE VI

500 mg of thalidomide and 60 mg of prednisone are mixed. The active ingredients are tritrated and as with lactose to selected capsule size.

Although only a few exemplary embodiments of this invention have been described in detail above, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention.

WHAT IS CLAIMED IS:

1. A method for the treatment of rheumatoid disorders which comprises administering to a patient in need of such treatment, a daily dosage form during an uninterrupted consecutive sequence of 365 days, and in accordance with the following regimen: (a) a three time a day, oral dose in an uninterrupted consecutive sequence of not more than 365 days of a tumor necrosis factor inhibitor compound effective in the treatment of rheumatoid disorders in dosage amounts not to exceed 900mg per day or until RF, ESR and/or AI have decreased or returned to normal, and (b) a daily, oral dose in uninterrupted consecutive sequence after cessation of said regimen (a) of a tumor necrosis factor inhibitor compound effective in the treatment of rheumatoid disorders in dosage amounts of between 50mg/week and 100mg/day, indefinitely, or until RF, and/or AI stabilize or normalize.

2. The method of claim 1 wherein said tumor necrosis factor inhibitor compound is selected from the group consisting of thalidomide, pentoxifylline and xanthines.

3. The method of claim 2 wherein said tumor necrosis factor inhibitor compound is thalidomide.

4. The method of claim 1 further including a compound selected from the group consisting of non-steroidal anti-inflammatories, steroidal anti-inflammatories, gold salts, penicillamines or mixtures thereof.

5. A pharmaceutical composition comprising thalidomide and an pharmaceutical acceptable carrier wherein said thalidomide has a particle size of less than one micron.

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6. A pharmaceutical composition comprising: (a) thalidomide; (b) a non-steroidal anti-inflammatory carboxylic acid selected from the group consisting of the aryl acetic acids, the aryl propionic acids, the fenamic acids, the biphenyl carboxylic acids, and the diphenyl ether carboxylic acids; and (c) a pharmaceutical inert carrier.

7. The composition of claim 6 wherein the non-steroidal anti-inflammatory carboxylic acid is an aryl propionic acid.

8. The composition of claim 7 wherein said aryl propionic acid is ibuprofen.

9. The composition of claim 7 wherein said aryl propionic acid is naproxen.

10. The composition of claim 7 wherein said aryl propionic acid is ketoprofen.

11. The composition of claim 7 wherein said aryl propionic acid is fenoprofen.

12. The composition of claim 7 wherein said aryl propionic acid is flurbiprofen.

13. The composition of claim 6 wherein said non-steroidal anti-inflammatory carboxylic acid is an aryl acetic acid.

14. The composition of claim 13 wherein said aryl acetic acid is indomethacin.

15. The composition of claim 14 wherein said aryl acetic acid is sulindac.

16. A pharmaceutical composition comprising: (a) a tumor necrosis factor inhibitor; (b) a compound selected from the group consisting of (i) non-steroidal anti-inflammatory carboxylic acids; (ii) steroidal anti-inflammatories; (iii) gold salts and (iv) penicillamines; and (c) a non toxic pharmaceutical inert carrier.

17. The compositions of claim 16 wherein said tumor necrosis factor inhibitor is pentoxifylline.

18. The composition of claim 16 wherein said tumor necrosis factor inhibitor is thalidomide and said steroidal anti-inflammatory is a prednisone.

19. The composition of claim 16 wherein said TNF inhibitor is thalidomide and said gold salt is auranofin.

20. The composition of claim 16 wherein said TNF inhibitor is thalidomide and said non-steroidal carboxylic acid is flufenamic acid.